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RESEARCH NEWS

Bridging the gap toward understanding short-term synaptic plasticity

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***JGP* study explores a new way to conceptualize an enduring neuronal mystery.**

In neurons, the arrival of an action potential at a synapse causes an influx of calcium, followed by fusion of neurotransmitter-containing synaptic vesicles with the plasma membrane. Released neurotransmitters diffuse across the gap between cells and activate receptors on the postsynaptic cell, evoking an electrical response whose strength is dictated by how much neurotransmitter was released. Interestingly, when a presynaptic cell receives a train of action potentials at the synapse, the intensity of subsequent postsynaptic responses does not always match that of the first. This phenomenon, called short-term synaptic plasticity, is poorly understood. In this issue of the *Journal of General Physiology*, Pulido and Marty present a model that may help explain how short-term synaptic plasticity comes about (1).

Short-term synaptic plasticity results from changes in the behavior of the presynaptic cell. It can manifest as either depression, where the postsynaptic response to each action potential in a train grows progressively weaker, or facilitation, where each action potential evokes a progressively stronger response.

"There is a little stockpile of synaptic vesicles that you have at the start of a train stimulation. Once they are gone, the synapse has to depress because it doesn't have enough synaptic vesicles," explains Alain Marty, Research Director Emeritus at Paris Descartes University. In contrast, facilitation occurs because of progressively increasing calcium levels at the synapse. "We think that what calcium does is bring vesicles to the plasma membrane. In a way, facilitation is just increasing the number of vesicles that are ready to fuse—the exact opposite of depression."

To fuse and release neurotransmitter, a synaptic vesicle must first be docked at one of a limited number of specialized fusion sites at the presynaptic plasma membrane (2). Therefore, vesicle release depends on docking site occupancy, which in turn is governed by whether a vesicle is docked, how likely it is to fuse, and how quickly a new vesicle can be recruited from the synapse's vesicle reserves to refill an empty docking site. Tweaking any of these three properties can alter whether a synapse is depressing or facilitating, as can be demonstrated when these variables are incorporated into a simple mathematical model. However, this model predicts that a synapse that starts out depressing or facilitating will remain so throughout an action potential train. This fails to account for a host of experimental observations showing that synapses can start out being facilitating, but then switch to depressing behavior mid-train.

Camila Pulido and Alain Marty recorded from single synapses in molecular layer interneurons (right) and paired this data with mathematical modeling to probe the nature of short-term synaptic plasticity. Photos courtesy of the authors.

"We have also sometimes observed a strange sequence: depression followed by facilitation," says Marty. Graduate student Camila Pulido encountered this pattern while making electrophysiological recordings at single synapses between rat cerebellar molecular layer interneurons (MLI; 3).

"In the beginning, we tried to ignore this, but then we started studying it," says Marty. Such behavior has only rarely been observed in the past (4).

Importantly, prior work by Marty's group (3, 5) had hinted that synaptic vesicles might occupy a "predocked" state before reaching a plasma membrane docking site. This would affect the likelihood that a docking site is occupied. When Pulido and Marty incorporated a predocked state into their mathematical model, they found the model could still faithfully describe straightforward depressing-only or facilitating-only synaptic behavior, but was now also able to predict both facilitating/depressing and depressing/facilitating behaviors. The researchers validated their model by exploring what conditions are required to reproducibly evoke depressing/facilitating behavior at MLI–MLI synapses.

"Our work suggests that changes in synaptic strength during a train primarily reflect changes in docking site occupancy," notes Marty. He hopes researchers will consider this new model for explaining short-term synaptic plasticity in their work, and be inspired to identify the molecular basis of the hypothesized predocked state.

1. Pulido, C., and A. Marty. 2018. *J. Gen. Physiol.* https://doi.org/10.1085/jgp.201812072
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3. Pulido, C., et al. 2015. *Neuron.* 85:159–172.
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5. Miki, T., et al. 2016. *Neuron.* 91:808–823.

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